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WHAT IS THE IMPACT OF BRAIN AND EXTREMITY INCLUSION IN THE IMAGING OF MALIGNANT MELANOMA WITH F-18 FDG PET/CT?

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Student number: 676331

A Research Report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfillment of the requirements for the degree of Master of Medicine in the branch of Nuclear Medicine

Johannesburg

October 2016

Candidate's declaration

I, Olwethu Natash Mbakaza, declare that this research report is my own work. This research report is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



Dr. Olwethu Mbakaza

October 2016

Master of Medicine in the branch of Nuclear Medicine

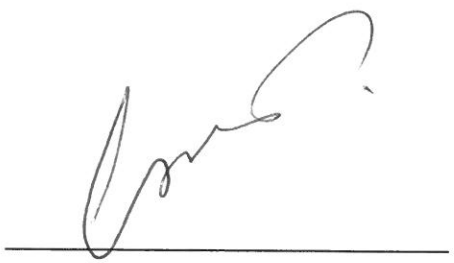
October 2016

To whom it may concern:

Re: Dr. Olwethu Mbakaza
Student number: 676331
Staff number: A0027196
MMed Nuclear Medicine

This letter is to certify that Dr. Olwethu Mbakaza has done her research in Nuclear Medicine. Her topic is **"What is the impact of brain and extremity inclusion in the imaging of malignant melanoma with F-18 FDG PET/CT?"** She compiled and analyzed the data herself and followed the protocol for her study accordingly. The entire research article was written by herself with assistance from her supervisor.

Kind regards,



Prof MDTHW Vangu
Head of Radiation Services
Head of division Nuclear Medicine

Dedication

This thesis is dedicated to my husband, Mbaliso, for his unwavering support, mentorship, exemplary leadership and most importantly, his unfailing, ever-constant love for me. You epitomize the meaning of priesthood. I love you, always, forever. I know that I'm God's favourite, simply, because He gave you to me.

My lovely daughter, Wela; never have I seen such a beautiful face before. You light up my life. Mommy loves you immeasurably.

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The author would like to acknowledge the following people, who have contributed to making this thesis a success:

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- NHLS staff for your assistance with data collection.
- My extended family for always being so supportive in my academic pursuits.

The Lord my God

...who crowns me with loving kindness and tender mercies.

Who satisfies my desires with good things, so that my youth is renewed like the eagle's (Ps 103:4-5).

Thank you, Father for all you have done for me.

Abstract

Objectives: This study aimed to ascertain if there is any clinical value in including brain and extremities in the ^{18}F-FDG PET/CT imaging of patients with malignant melanoma.

Methods: This was a retrospective study done at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Johannesburg. All consecutive ^{18}F-PET/CT reports for patients referred to the CMJAH department of Nuclear Medicine for an ^{18}F-FDG PET/CT study, spanning from 01 January 2008 to 31 December 2013, who have histologically proven malignant melanoma were included in the study. The prevalence of brain and extremity lesions on ^{18}F-FDG PET/CT reports was documented. Hospital records were reviewed to see if clinical or histological correlation was done for lesions that were likely malignant; and to also review the impact of ^{18}F-FDG PET/CT findings on patient management.

Results: One hundred and fifty nine ^{18}F-FDG PET/CT studies in 121 patients were included for assessment. The median patient age was 54 years (ranging from 16 – 84 years). Eighteen patients (12%) had lesions in the brain, eight (5.33%) of which were classified as likely benign, five (3.33%) of which were classified as likely malignant, and five (3.33%) of which were classified as indeterminate. However, nine (5.7%) patients in the whole group did not have brain acquisition and were excluded from the assessment. None of the patients with likely malignant or indeterminate brain lesions underwent further investigation such as a radiological correlation with MRI or a pathological correlation. Three patients had change in management as a result of findings of brain lesions on ^{18}F-FDG PET/CT. One patient had radiotherapy to the brain with steroids, in addition to their chemotherapy regimen; another had

whole brain palliative radiotherapy, in addition to their chemotherapy regimen; and the last patient had changes made to their chemotherapy regimen to a different regimen.

Thirty six patients (37%) had lesions in the extremities, three (8%) of the 36 were classified as likely benign, six (17%) of which were classified as likely malignant, and two (6%) of which were classified as indeterminate. The remaining twenty five (69%) had their primary tumour in the extremities. However, 61 (38%) patients in the whole group did not have acquisition of the extremities. Ninety eight patients had extremity scans. None of the patients with extremity lesions underwent further radiological and or pathological correlation, and none had a change in stage or change in clinical management.

Conclusion: Our study showed that although there was no change in the clinical staging resulting from the acquisition of extra brain and extremity views on ^{18}F-FDG PET/CT, there was a change in the clinical management of those with brain lesions. There was no change in clinical management of those patients with extremity lesions. The suggested protocol is acquisition of brain views only in patients with additional metastatic lesions after the acquisition of the whole body view (base of skull to mid-thigh)

This protocol, however needs validation with a more comprehensive, prospective study.

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Nomenclature and Abbreviations

^{18}F-FDG PET/CT	Fluorine – 18 Fluorodeoxyglucose Positron Emission Tomography/ Computed Tomography
ABCD	Asymmetry; Border; Colour; Dimension; Evolution
AJCC	American Joint Committee on Cancer
TNM	Tumour Node Metastases
SNB	Sentinel Node Biopsy
MRI	Magnetic Resonance Imaging
FNA	Fine Needle Aspiration
LDH	Lactate Dehydrogenase
LND	Lymph node dissection
RT	Radiotherapy
T-VEC	Talimogene laherparepvec
BCG	Bacillus Calmette-Guerrin
IFN	Interferon
IL-2	Interleukin-2
Anti-PD-1	Anti-programmed cell death protein 1

CHAPTER 1

Introduction

1.1 Background

Malignant melanoma is a malignancy of the melanocytes, the cells that produce pigment, which occur largely in the skin, but also located in the eyes, ears, gastrointestinal tract, oral and genital mucosa; and leptomeninges (1). The incidence of malignant melanoma has increased in the United States over the years (2), and, with an improved life expectancy in the elderly, it is said that would be a challenge in public health. (3). According to the South African national cancer registry from 2011, the age-adjusted incidence for all population groups in males was 4.23/100 000; and in females was 2.77/100 000 (4). The lifetime risk of developing malignant melanoma in South Africa in 2011 was 1 in 213 males and 1 in 341 females (4). Nuclear medicine plays a role in the management of the disease, and this includes imaging with ^{18}F- Fluoro deoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) to evaluate for the presence of distant metastases.

The standard oncology imaging protocol with ^{18}F-FDG PET/CT includes whole body imaging from the base of skull to the mid thigh. In malignancies with a known tendency to metastasize to the brain, additional images of the brain are acquired. In malignant melanoma, additional images of both the brain and the extremities (upper and lower) are added to the standard imaging protocol (5) and our institution is not an exception. This tends to be time consuming, and may limit the number of patients that can be imaged in a day. The impact of the inclusion of brain and extremities has

been recently questioned in literature, and a question of impact in the patient management has been raised (5).

1.2 Literature Review

1.2.1 Malignant melanoma: definition and incidence

Melanoma is the most malignant cancer of the skin. It develops from the melanin-producing cells in the skin, the melanocytes. Despite recent treatment advances, it is the kind of skin cancer that is most serious, with the most fatalities from any skin disease (6). Malignant melanoma accounts for not more than 5% of dermatologic malignancies, but it is considered as the main reason of about 60% of people dying from skin cancer (3). It is estimated that the incidence rate of melanoma may increase by 3-7% every year (7), and this has been attributed to greater public awareness and earlier and improved detection; and Bandarchi et al suggest that it is partly due to a true rise in incidence (1, 3, 7, 8). The highest incidence rate in the world is noted in Queensland, Australia (3). The incidence of melanoma has increased in people of Caucasian ethnicity (3). In individuals with dark-skin, the same incidence seems to be constantly lower (3). Every year, about 2-3/100 000 deaths are estimated to be due to melanoma, and in 2010, the mortality rate was said to have been increasing in males over the last 25 years (9).

It typically occurs in a Caucasian adult male or female in the 4th decade of life (3). In a typical patient, the lesions occur on the leg and back in females and males respectively (3).

Malignant melanoma has four major types (10).

- It is said that superficial spreading melanoma occurs more often than any other subtype, and it typically occurs to skin exposed to sunlight.
- Nodular melanoma grows quickly into the dermis as compared to other types and feels like a firm, dome-shaped bump.
- Acral letiginous melanoma is the least common type, occurs mostly in darker coloured skins and is typically found on the palms of the hands and soles of the feet.
- Lentigo maligna melanoma grows slower than the other types of melanoma, and is not associated with moles. It looks likens to a stain with uneven edges. Occurs in the face and arms of older people.
- Mucosal melanoma: including ocular and sinonasal melanoma is a rare form, accounting for about 1% of melanoma cases. It is considered not to be associated with UV exposure or any risk factors, and as a result, most cases are quite advanced once identified (11)

1.2.2 Clinical features

The first sign of melanoma is a mole on the skin that looks abnormal (6)

The ABCD rule was developed in 1985 to provide members of the public and primary care physicians with a practical acronym for gross inspection of a pigmented lesion for early recognition of malignant melanoma (12). It was then revised to ABCDE in 2004 to emphasize that evolution of the lesion is an important criterion used to differentiate malignant melanoma from benign pigmented lesions.

The ABCDE rule represents (12):

A: Asymmetry: One side of the lesion not being the same as the other side.

B: Border: A lesion with an irregular border

C: Colour: A lesion that has different shades of colour, including brown, tan, blue, black

D: Dimensions: Melanomas are often > 6mm in diameter

E: Evolving: A lesion that has changed in size, colour, shape and texture over the last few weeks or months.

Risk factors include age, exposure to ultraviolet radiation, multiple or atypical moles, family history, fair complexion, xerodermal pigmentosum and immune suppression (10).

Multiple benign or atypical nevi, together with a family history of melanoma constitute the strongest risk factors for melanoma (10). There are some other factors to be considered such as immunosuppression, ultraviolet radiation exposure and sensitivity to the sun. The latter have been considered to play a role and can be linked to genetic predisposition or an environmental stressor (8).

There are three well-defined metastatic pathways of melanoma metastases. They include local extension via satellite metastases or in-transit metastases; disease extending to lymph nodes in a particular region; and distant disease to other organs, being visceral or not (13).

More than eighty percent (82 – 85%) of patients with malignant melanoma are estimated to present with disease that is localized, about one out of 10 patients (10 - 13%) with regional disease and 2-5% with distant metastatic disease (10). Patients

with a primary cutaneous melanoma thickness of less than 1 mm have a greater than 90% ten year survival. Those with a primary lesion thickness more than 4 mm have a poor prognosis with a 4-year survival of 40% (13, 14). Patients frequently present with metastatic disease even after potentially curative surgery has been performed, due to early haematogenous spread (14). Disease that is spread may be seen in other cutaneous or subcutaneous sites, brain lung, liver, gallbladder, spleen and distant lymph nodes.

1.2.3 Diagnosis

The clinical examination with emphasis on the ABCDE features as stated above, is the first step to the diagnosis of malignant melanoma. Common early warning signs and symptoms which should be looked out for include pruritus, ulceration and bleeding in a mole (2). Dermoscopy by an experienced physician boosts clinical suspicion and enhances diagnostic accuracy in diagnosing malignant melanoma (3). However, definitive diagnosis is made by performing a full thickness excisional biopsy, with complete removal of the lesion suspected of being a melanoma, with a vertical and horizontal margin (2).

1.2.4 Staging

The American Joint Committee on Cancer (AJCC) staging system should be followed on the histology report, including the maximum thickness of the tumor from the granular cell layer in the epidermis to the deepest malignant cell in millimeters (Breslow's measurement), level of invasion (Clark level I–V), presence of ulceration, presence and extent of regression and clearance of the surgical margins (9).

Breslow thickness is the measurement of melanoma depth from the epidermal basement membrane to the deepest melanoma tumour cells (7). It is the most critical factor in the determination of prognosis for melanoma, as deeper melanoma are more prone to haematogenous and lymphogenous metastases (7). This measurement technique for the determination of lesion depth was first described by Alexander Breslow in 1970 (15). Breslow's depth was divided into 5 stages, as stated in Table 1. The recommendation is to completely remove the lesion primarily because the Breslow's thickness measurement is an important prognostic factor that determines whether lymph node dissection is appropriate or not; and whether adjuvant therapy is required (2).

Table 1: Breslow's Depth

Stage	**Depth**
I	Less or equal to 0.75 mm
II	0.76 mm – 1.50 mm
III	1.51 mm - 2.25mm
IV	2.26 mm - 3.0mm
V	Greater than 3.0 mm

Adapted from Alexander Breslow. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Annals of surgery, 1970.

The Clark level of invasion measures the depth of penetration of the melanoma in the skin (16). It describes the extent of anatomical involvement within the cutaneous and subcutaneous structures (15), as described in Table 2.

Staging of malignant melanoma follows the tumour (T), node (N) and metastases (M) classification for malignancies [Table 3]. The 2010 American Joint Committee on Cancer uses the following guidelines for staging malignant melanoma (17) [Table 4].

Table 2: Clark level of invasion

Level of invasion	
I	Tumour is confined to the epidermis, with an intact basement membrane
II	Invasion of tumour into the papillary dermis
III	Involvement filling the papillary dermis and involvement of the junction between the papillary and reticular dermis
IV	Invasion of tumor into the reticular dermis
V	Invasion of tumour cells into the subcutaneous tissue

Adapted from Wallace H. Clark et al. The Histogenesis and Biologic Behaviour of Primary Human Malignant Melanomas of the skin. Cancer Research, 1969

Table 3: TNM Staging

Tumour (mm)	**Tx**	**T0**	**T1s**	**T1**	**T2**	**T3**	**T4**
	Primary tumor cannot be assessed (e.g. curettage or severely regressed melanoma)	No evidence of primary tumor	Melanoma in situ	≤ 1.0 mm thickness	1.01–2.0 mm	2.01–4.0 mm	>4.0 mm
				a:without ulceration and mitosis <1/mm^2 b:with ulceration or mitoses ≥ 1/mm^2	a:without ulceration b:with ulceration	a:without ulceration b:with ulceration	a:without ulceration b:with ulceration
Nodes	**Nx**	**N0**	**N1**	**N2**	**N3**		
	Patients in whom the regional nodes cannot be assessed (e.g., previously removed for another reason)	No regional metastases	1 node	2-3 nodes	4 or more metastatic nodes, or matted nodes, or in transit met(s)/ satellite(s) with metastatic node(s)		
Metastases	**M0**	**M1a**	**M1b**	**M1c**			
	No detectable evidence of distant metastases **Normal LDH**	Metastases to skin, subcutaneous, or distant lymph nodes **Normal LDH**	Metastases to lung **Normal LDH**	Metastases to all other visceral sites **Normal LDH** Distant metastases to any site **Elevated LDH**			

As adapted from the AJCC Cancer Staging Manual, 7th edition, 2010

Table 4: Clinical and Pathological Staging

	Stage	T	N	M
Clinical Stage and Pathologic Stage	0	is	0	0
	IA IB	1a 1b 2a	0 0 0	0 0 0
	IIA IIB IIC	2b 3a 3b 4a 4b	0 0 0 0 0	0 0 0 0 0
Clinical Stage Pathologic Stage	III IIIa IIIb IIIc	Any T T1 – T4a T1 – T4b Any T	>/-N1 N1a and N2a N1a, N2a, N1b, N2b, N2c N3	M0 M0 M0 M0
Clinical and Pathologic Stage	IV	Any T	Any N	M1

As adapted from the AJCC Cancer Staging Manual, 7th edition, 2010

1.2.5 Work-up and Management of malignant melanoma

The work-up and management of malignant melanoma largely relies on the stage of disease (6, 17). In low-risk melanomas (pT1a), no further investigations are necessary, although in stages IA, together with IB, sentinel lymph node biopsy could be considered (17). In the above-mentioned stages, imaging is only used to evaluate

specific signs and symptoms. In stages IB – IIA, ultrasonography to detect locoregional lymph node metastases is recommended (18). The latest European Society for Medical Oncology clinical practice guidelines also recommend staging with CT or PET/CT prior to surgical treatment and sentinel node biopsy for tumour stages > pT3a (18).

In stage III positive sentinel lymph nodes, baseline imaging with CT, MRI or PET/CT could be considered for staging and for the evaluation of specific signs and symptoms (17). In stage III disease with clinically positive lymph nodes, FNA if feasible or core, incisional or excisional biopsy is recommended; and for in-transit lymph nodes of the same stage, baseline imaging for staging is recommended. In stage IV metastatic disease, biopsy is preferred over FNA if archival tissue is not available for genetic analysis, measurement of serum LDH; and chest, abdominal and pelvic CT scan, brain MRI with or without PET/CT for baseline imaging (17).

The investigation of suspected recurrence is outlined in Table 9

Table 5: Investigation of suspected recurrent disease

Recurrence status	**Work-up**
Persistent disease or true local scar recurrence	• Biopsy to confirm • Work-up appropriate to primary tumour characteristics
Local, satellite, and/ or in-transit recurrence Nodal recurrence Distant metastatic disease	• FNA if feasible or core, incisional or excisional biopsy • Recommend baseline imaging for staging and to evaluate specific signs and symptoms (CT; PET/CT; MRI) • FNA preferred, if initial resection is planned. Biopsy preferred if initial therapy is to be systemic • LDH • Recommend chest/abdo/pelvic CT, brain MRI +/- PET/CT for baseline imaging and to evaluate specific signs and symptoms

As adapted from the NCCN Guidelines for Melanoma version 2.2016

1.2.6 Treatment of malignant melanoma

1.2.6.1 Localized and locoregional disease

The recommendation, according to the latest European Society for Medical Oncology clinical practice guidelines is wide local excision with safety margins on 0.5 cm for melanomas in-situ; 1 cm for melanomas with up to 2 mm thickness; and 2 cm for thicker melanomas (18). Modifications with reduced safety margins are permissible for acral and facial melanomas for preservation of function; and this should be carried out with micrographic surgery (18). In melanoma with tumour thickness of > 0.75 mm and > 1mm, ulceration or mitotic rate; sentinel lymph node biopsy is recommended for precise staging. In a case with positive sentinel lymph node biopsy, complete lymphadenectomy of regional lymph nodes; which offers relapse-free survival and not proven to offer overall survival must be discussed with the patient (18).

Adjuvant therapy with in high risk primary melanomas (stage IIB/C) or completely resected lymph node metastases has been discussed extensively by various clinical trials, particularly low, intermediate and high dose interferon-α (IFN-α).
A meta-analysis showed statistically significant improvement in disease free and overall survival, with no clear recommendation of a dose or duration of therapy. The European Organisation for Research and Treatment of Cancer (EORTC) has initiated a large prospective randomized trial to investigate the protective effect of pegylated interferon-α-2b (PegIFN-α-2b) in the adjuvant setting, since it is suitable

for long-term therapy. The results of a large randomized trial showed that interferon-α therapy had a significant impact on relapse-free survival, disease free survival and overall survival. They recommended that in patients with micrometastases and primary ulcerated melanomas, PegIFN-α can be recommended in this group of patients if tolerated well. In stage IIIB and higher, participation in clinical trials should be encouraged.

Surgical removal or stereotactic irradiation of locoregional recurrence or single distant metastasis should be considered in fit patients, as a therapeutic option, offering potential for long-term disease control.

1.2.6.2 Treatment of systemic metastatic disease (stage IV)

The treatment of metastatic disease depends on whether it is limited or disseminated (6). Surgical resection is the best choice of management for limited disease. In tumour that is unresectable, observation or systemic therapy could either be first-line or second-line. First-line therapy includes, immunotherapy, targeted therapy if BRAF mutated or participation in clinical trial (6). Second-line or subsequent therapy is employed where there is disease progression or maximum clinical benefit from BRAF targeted therapy, and this includes anti-PD-1 monotherapy, targeted therapy of BRAF mutated, IL-2, biochemotherapy, cytotoxic agents, imatinib for tumours with activating mutations of C-KIT (6).

Disseminated disease without brain metastases is preferably treated with systemic therapy; by enrolment in a clinical trial; with T-VEC; and /or palliative resection

and/or radiotherapy for patients who are symptomatic or providing the best supportive care (6). If there is disseminated disease with brain metastases, palliative resection should be considered and/or radiotherapy (6).

Immunotherapy

Immunotherapy employs the use of activating an immune response to suppress tumour development (19).

Current immunotherapy approaches fall in the following main categories (20):

Checkpoint inhibitors:

- PD-1 inhibitors (Pembrolizumab or Nivolumab) target PD-1, a cell surface receptor expressed on T-cells that down regulates the immune system by preventing the activation of T-cells hence boosting the immune response against melanoma cells.
- CTLA-4 inhibitors (Ipilimumab) block CTLA-4, a protein receptor that functions as an immune checkpoint downregulating immune responses.

Oncolytic virus therapies:

- Talimogene laherparepvec (Tvec) is an oncolytic virus that can be used to replicate within tumour cells resulting in systemic antitumour responses (21).

BCG vaccine that works by activating the immune system. Others include cytokines (interleukin 2 and interferon alpha); adoptive cell therapy and monoclonal antibodies (20).

Role of BRAF inhibitors in V600 mutated tumours

Activating BRAF mutations occur in approximately 50% of malignant melanomas, and among those, about 90% occur at codon 600 (22). The most frequent BRAF mutation is V600E, and it has been implicated in the progression of melanoma. These mutations are most common on skin without chronic sun-induced damage (22). Several BRAF inhibitors have been developed such as sorafenib, vemurafenib – the latter which has been approved by the US food and drug association for unresectable or metastatic melanoma with the V600E mutation. Vemurafenib was tested in a 2 arm phase III trial which compared it to decarbazine chemotherapy. The results showed a relative reduction of 63 % in the risk of death and of 74 % in the risk of tumor progression in patients (22). The median overall survival for the vemurafenib arm was of 13.2 months compared to 9.9 months in the dacarbazine arm.

Patients with metastatic melanoma should preferably have metastasis or the primary tumour screened for detection of BRAFV600 mutation. Treatment options for the first- and second-line setting include anti-PD1 antibodies (pembrolizumab, nivolumab), ipilimumab, an anti-CTLA4 antibody, for all patients, and BRAF/ inhibitor combinations for patients with BRAF-mutant melanoma. If clinical trials or the approved new targeted compounds are not available, cytotoxic drugs such as DTIC or temozolomide may be administered, with modest activity shown.

Lack of efficacy of cytotoxics

Systemic therapy for melanoma includes chemotherapy, radiation and immunotherapy, none of which have proven long-term efficacy, with significant toxicities and side effects (23). The response rate of Decarbazine, the first line choice in advanced melanoma, is 10-20%, and tumour relapse is reported occur 5-6 months after treatment. Cytotoxic drugs exert their toxicity mainly by inducing DNA damage, followed by cell apoptosis (23). Melanoma cells are resistant to chemotherapy induced cell-death (23). The possible explanations include disrupted accumulation of agents caused by drug pumps, upregulated DNA repair, defective apoptosis signaling, and survival factor activation. However the mechanism of chemoresistance is unknown (23).

1.2.7 Role of F-18 FDG PET/CT in malignant melanoma

Positron emission tomography (PET) is a non-invasive imaging modality that provides 3 -dimensional tomographic images and quantitative analysis of perfusion, cell metabolism and viability (24). ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) has largely replaced ^{18}F-FDG PET alone due to lack of anatomical localization of the latter, leading to false negative and false positive results (25).

A systematic review of the potential patient-relevant benefit of ^{18}F-FDG PT/CT in the primary staging of melanoma found no evidence of patient-pertinent value in primary staging, and that the accuracy of diagnosis of ^{18}F-FDG PET/CT increased with higher AJCC stages (26). A prospective, multicenter Ontario PET registry study showed that there was a significant upstaging after ^{18}F-FDG PET/CT, with increase

in the upstaging to M1 status, and no patients being downstaged (27). This upstaging also had a significant relationship with change in management, especially with patient groups who require surgical resection of metastases distant to the primary melanoma site (27).

It is a particularly useful functional imaging modality in the staging of advanced disease and high risk melanoma (27), and shows a potential ole in assessing therapeutic response (28). ^{18}F-FDG PET/CT has a limited role in patients with early stage disease with no nodal or distant metastases, but has proved useful in patients with distant nodal metastases (28, 29). It characterizes lesions that are indeterminate on CT Scan (10), with a significant influence on management, recurrence and follow-up (25). In patients with suspicion of recurrence, it is an invaluable tool in restaging of locoregional recurrence, with alteration of patient management. A study undertaken to evaluate the utility of ^{18}F-FDG PET/CT in the surveillance of patients with microscopic and macroscopic stage 3 disease, found that it is a tool that is useful in the surveillance of patients with macroscopic disease (31). However, the utility of ^{18}F-FDG PET/CT still needs to be validated further in larger prospective trials when patients initially present with microscopic stage 3 disease (31). The ^{18}F-FDG PET/CT protocols for imaging malignancies are not standardized, and have institutional variation, with the most commonly used field of view being imaging from the base of skull to the mid-thigh (32). The acquisition of the scan is done with five to seven bed positions at 3–5 minutes per bed position, where each patient is scanned at a time interval between15 and 25 minutes (5). Because of its propensity to metastasize to any region, the protocol for imaging melanoma includes the brain, upper and lower extremities. Recent studies, however have questioned the clinical

significance of including the above regions (5). This protocol requires the scan to be extended to an extra six to seven bed positions, which almost doubles the scanning time for emission to achieve true whole-body images, with an added disadvantage of an increased radiation exposure related to the transmission CT scan used for anatomical localization and attenuation correction, particularly in patients in whom repeated scans are required for the purposes of surveillance (5).

1.2.8 Role of F-18 FDG PET/CT imaging of the brain and extremities in malignant melanoma

There have been several studies conducted to establish the role of the standard melanoma acquisition parameters (i.e. including brain and extremities), with some reaching the same or similar consensus. Lazaga et al, as quoted in the Clinical Nuclear Medicine Journal in 2010, did a retrospective review of 200 consecutive whole body ^{18}F-FDG PET/CT scans in patients with histological confirmation of malignant melanoma of the upper body (33). The objective of their study was to evaluate clinically pertinent findings in the lower extremities in patients with malignant cutaneous melanoma who have been imaged from the base of skull to the feet and what diagnostic and prognostic information these findings added (33). Their study was also performed to establish a confidence interval that would support exclusion of lower-extremity views in these patients (33). Their results found that 1 out of 200 patients had a true positive metastasis in the lower extremity, concurrent with extensive upper body metastatic disease, however the location of the lesion was in the upper femur, which is included in the standard field of view. One patient had a false positive benign inflammatory lesion, and one patient was incidentally found to

have squamous cell carcinoma (33). They stated that they are 95% confident that if they exclude the lower extremities, there would be a range of between 0% and 1.88% in the proportion of missed lower extremities lesions (33).

Another study conducted to evaluate the therapeutic impact of including the lower limbs in the imaging of melanoma with ^{18}F-FDG PET/CT showed poor additional benefit, with none out of the 174 scans in 122 patients showing unexpected metastatic lower limb lesions (34). This study received a response form Davidson and Sundram that is quoted in the Nuclear Medicine Communications Journal in 2011, who also undertook a similar study with similar findings, citing that no guidelines exist citing the indications or the appropriateness of the acquisition of a half body ^{18}F-FDG PET/CT in malignant melanoma (35). They also wondered whether it would be acceptable if half-body imaging were to be considered for patients with melanoma in whom there is no strong suspicion of or known primary in the lower limb, citing several advantages of limited body over whole body imaging (35). Querellou responded to this letter by confirming that the ^{18}F-FDG PET/CT protocol had been changed in their centre, excluding the lower limb acquisition, also noting the useful gain in time especially for mobile PET/CT units (36).

Abdelmalik et al, in their work quoted in the Frontiers in Oncology Journal in 2013, argue in their publication that the standard field of view for imaging using ^{18}F-FDG PET/CT in oncology is limited and may underestimate the extent of metastatic involvement to the areas beyond the routinely used field of view (32). They went on to propose in their study the inclusion of the brain in the field of view, as their findings

had significant clinical impact on patient management. This inclusion of the brain however was not proven to affect management in a retrospective study by Niederkohr et al, as quoted in the Nuclear Medicine Communications Journal in 20007(5). The study involved a review of 296 ^{18}F-FDG PET/CT examinations for melanoma (5). In that study, only 25 scans showed brain/scalp abnormalities, of which only 4 were unanticipated abnormalities: 2 were false positive findings, and 2 were shown to represent metastatic disease in addition to numerous other metastases elsewhere in the usual field of view, an incidence rate that was lower than 1%. They saw lower extremity abnormalities in 59 of the 296 scans reviewed. Thirteen showed unanticipated equivocal or suggestive of malignancy: eight were shown to represent metastases, with additional multiple metastatic foci in other regions in the usual field of view; and five were proven to be false positive findings (5). There were no cases of unexpected solitary malignant lesions identified in the brain/scalp or lower extremities (5). They thus concluded that in patients who are not known with or suspected of having primary or metastatic melanoma with involvement of the head or extremities, including these regions on ^{18}F-FDG PET/CT has low yield and does not appear to offer much substantial additional benefit, as additional metastatic detection in these patients is unlikely to alter clinical management (5). They also affirmed the adequacy of the routine base of skull to mid-thigh views for this patient subset with melanoma. A similar conclusion was reached by other studies such as the ones conducted by Loffler et al and Tan and Chatterton involving 215 and 398 ^{18}F-FDG PET/CT studies respectively, as quoted in the Nuklearmedizin Nuclear Medicine Journal in 2003; and the Hellenic Journal of Nuclear Medicine in 2012 respectively (37, 38). Loffler et al found only 1 unexpected ^{18}F-FDG avid

manifestation in the leg, and recommended that only those patients with known melanoma restricted to the legs should have additional views of the lower extremities (37). Tan and Chatterton found unexpected abnormalities in the brain in 1%, and extremities in 1.2% of patients, citing a potential role of the extended field of view in patients with metastatic melanoma of unknown primary, particularly if finding the primary will affect management (38). None of the above studies found unexpected isolated lesions in the extended field of view. These studies pose a diagnostic question as to whether extending the usual field of view in melanoma patients adds any extra diagnostic information and more importantly if the extended protocol affects patient management.

Problem statement: The addition of the brain and extremities to the routine ^{18}F-FDG PET/CT imaging protocol of malignant melanoma is time-consuming and hence may limit the number of patients that can be imaged in a day. This retrospective study is done to establish if in our environment the clinical management of patients with malignant melanoma may be affected by the additional imaging of the brain and extremities. The ^{18}F-FDG PET/CT studies from 6 consecutive years (from 2008 to 2013) were reviewed to determine if there were unexpected sites of disease in the brain and extremities that would alter the management of the patients.

CHAPTER 2

Materials and methods

Ethics clearance was obtained from the University of Witwatersrand's Human Research Ethics Committee (HREC), ethics clearance number M140258 (Appendix 1).

Permission was obtained from the CEO of CMJAH for the use of hospital patients' information (Appendix 2).

2.1 Study Design

This is a retrospective study done at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

2.2 Study Objectives

This study aimed to ascertain if there is any clinical value in including brain and extremities in the ^{18}F-FDG PET/CT imaging of patients with malignant melanoma.

2.2.1 Primary Objective:

- To do an audit of how many patients with malignant melanoma have been imaged with ^{18}F-FDG PET/CT in our institution in the last 6 years (2008-2013), and determine the prevalence of brain and extremity lesions in these patients.

2.2.2 Secondary Objective:

- To review the potential clinical impact of imaging brain and extremities in the management of patients with abnormal findings.

2.3 Study Population

All consecutive ^{18}F-FDG PET/CT reports for patients referred to the CMJAH department of Nuclear Medicine for an F-18 FDG PET/CT study, spanning from January 2008 to 31 December 2013, who have histologically proven malignant melanoma were included in the study. The indications for ^{18}F-FDG PET/CT referral were for staging, restaging, or suspected metastatic disease. A total of 159 studies in 121 patients were reviewed. Ultimately, 150 were included for brain assessment (Group 1), because nine patients did not have brain imaging included in their acquisition. Ninety eight out of 159 studies were included for the extremity assessment (Group 2) for the similar reason.

2.3.1 Inclusion criteria

- Patients with malignant melanoma referred for an ^{18}F-FDG PET/CT study for staging
- Patients who had imaging of the brain and extremities (Upper and lower limbs)
- Patients with suspected metastatic disease

2.3.2 Exclusion criteria:

- Patients with known metastases to the brain before ^{18}F-FDG PET/CT imaging

2.4 Imaging protocol, data processing and data collection

All patients are routinely instructed to fast for six hours and a ^{18}F-FDG injection is administered at a dose between 185 – 370 MBq. Prior to ^{18}F-FDG administration, glucose is measured with the use of an Accu-Chek Active glucose meter and glucose strips and a finger prick.

PET/CT scans were acquired using a Siemens Biograph 40 TruePoint PET/CT scan, which has an integrated 4-slice CT scan. The patients were scanned approximately 60 minutes following intravenous administration of 370 MBq of ^{18}F-FDG. A contrast or non-contrast CT scan was acquired first, for attenuation correction and anatomical localization of FDG activity. An emission scan was acquired afterwards. Both acquisitions image from the base of skull to the mid-thigh, which is known as the "whole body" acquisition, in the supine position, with arms raised above the head. The additional views included the brain, upper and lower limbs (also known as the extremities). The fused ^{18}F-FDG PET/CT images were then reviews in the 3 planes – the sagittal, coronal and transaxial planes.

2.5 Data analysis

The reported findings on ^{18}F-FDG PET/CT in the brain and extremities were documented. These were tabulated, in terms of presence or absence of lesions. Positive findings were further classified according to status, whether they were likely benign, likely malignant, indeterminate or acquisition not done; with the site of primary lesion being an additional classification for lesions in the extremities. The presence of other metastases in addition to documented brain or extremity lesions were documented; and the additional sites of metastases were classified according to number of lesions as less than 5, between 5 and 10, and more than 10 additional lesions.

Other variables that were tabulated include the patient's age, gender, ethnicity, site of primary lesion, time interval between scans (for patients who had more than one scan) and the tumour, node and metastases (TNM 2010) classification.

The hospital records of those patients with documented positive findings in the brain and extremities were reviewed to document whether correlation with either histology or conventional imaging modalities (CT or MRI) was done. The hospital records were also reviewed in order to determine management changes as a result of positive findings on ^{18}F-FDG PET/CT.

2.6 Statistical analysis

Data were analyzed using the IBM SPSS statistical analysis package, version 22.

For continuous variables the descriptive results were presented as medians and range (normal or not normally distributed). Categorical variables were summarized as frequencies and percentages.

Cross tables were generated to evaluate a relationship between variables, using the Fisher's exact test and the Pearson Chi squared test.

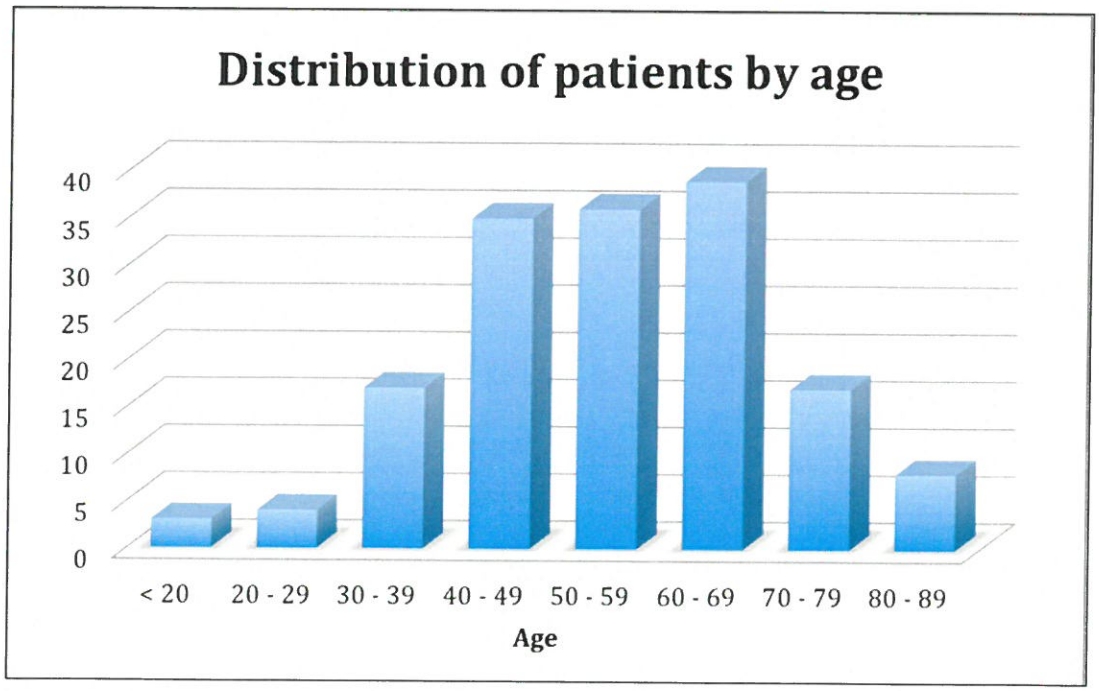
The strength or magnitudes of relationships were evaluated using the Phi and Cramer's V tests.

CHAPTER 3

Results

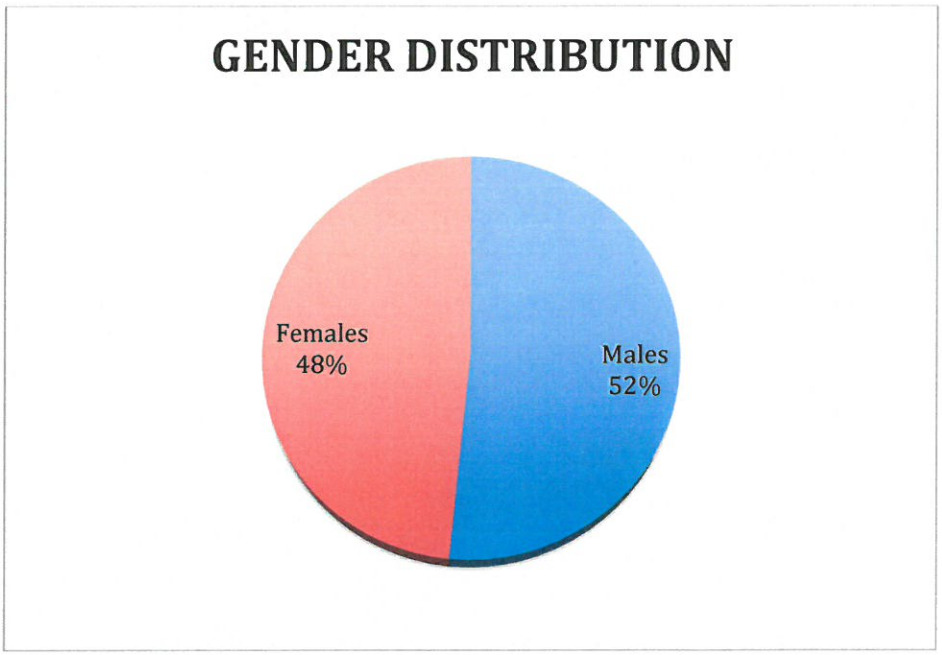
One hundred and fifty nine PET/CT studies in 121 patients were included for assessment. The distribution of primary sites is listed in Table 6. The median patient age was 54 years (ranging from 16 – 84 years). The distribution of patients by age and gender is stated in figures 1 and 2 respectively. Twenty-three patients had 2 or more ^{18}F-FDG PET/CT scans. The median time interval between scans was 10 months. The TNM stages are listed in Table 7.

Figure 1: Distribution of patients by age



Eighteen patients (12%) had lesions in the brain, eight (5.33%) of which were classified as likely benign, five (3.33%) of which were classified as likely malignant, and five (3.33%) of which were classified as indeterminate. However, nine (5.7%) patients in the whole group did not have brain acquisition. The ten (6.7% of total patients) who had likely malignant or indeterminate lesions all also had additional lesions that were classified as metastatic. Three of those ten (30%) with brain lesions but also with other metastases had less than five additional lesions, and seven (70%) had more than 10 additional lesions. While the likely benign brain lesions were considered as such on diagnostic CT, none of the patients with likely malignant or indeterminate brain lesions underwent further investigation such as a radiological correlation with MRI or a pathological correlation. The reasons why this was not done were unclear and not documented in the clinical notes.

Figure 2: Distribution of patients by gender



Three patients had change in management as a result of findings of brain lesions on ^{18}F-FDG PET/CT. One patient had radiotherapy to the brain with steroids, in addition to their chemotherapy regimen; another had whole brain palliative radiotherapy, in addition to their chemotherapy regimen; and the last patient had changes made to their chemotherapy regimen to a different regimen.

Table 6: Distribution of lesions by primary site

Primary site	Frequency (Percent)
Head and neck	20 (12.6)
Trunk	28 (17.6)
Upper extremities	15 (9.4)
Lower extremities	73 (45.9)
Other	5 (3.1)
Unknown/ not stated	18 (11.3)
Total	159 (100)

Thirty six patients (37%) had lesions in the extremities, three (8%) of the 36 were classified as likely benign, six (17%) of which were classified as likely malignant, and two (6%) of which were classified as indeterminate. The remaining twenty five patients (69%) had their primary tumour in the extremities but not an additional lesion. Out of the 11 with lesions in the extremities that were not the primary site of lesion, eight (73%) had likely malignant or indeterminate lesions and five of them

(63%) had additional lesions that were classified as metastatic. Two (25%) of these eight patients had less than five additional lesions; two (25%) had more than five but less than ten additional lesions; and one (13%) had more than 10 additional lesions. None of the patients with extremity lesions also underwent further radiological and or pathological correlation. None of the patients with extremity lesions had a change in stage or change in clinical management.

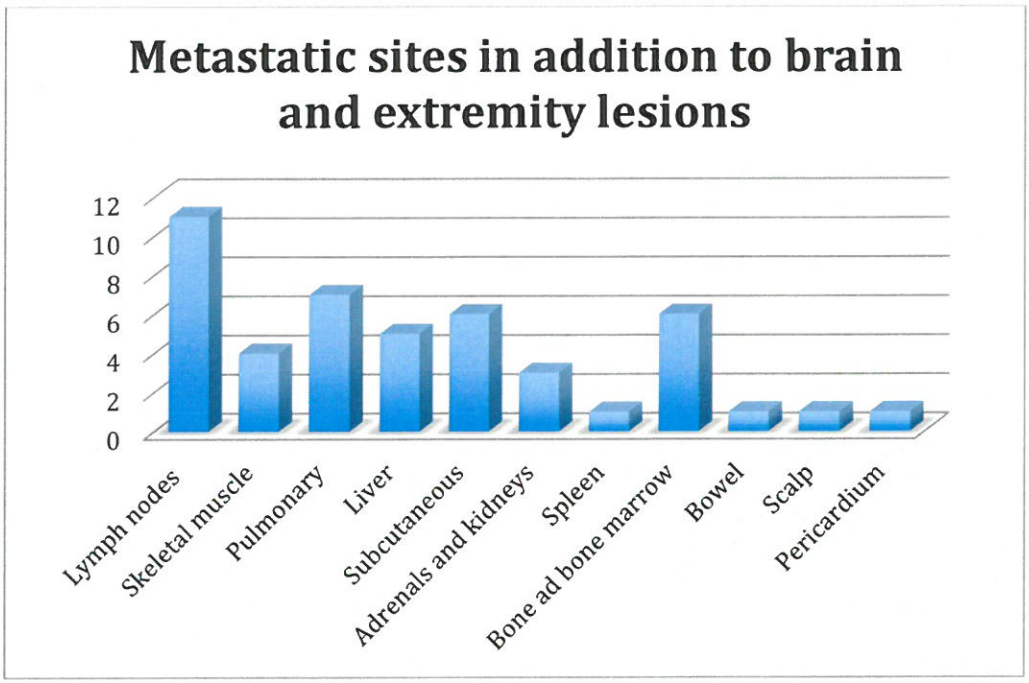
Table 7: Distribution of lesions by TNM stage

TNM Stage	Frequency (Percent)
Stage 1	5 (3.1)
Stage 2	25 (15.7)
Stage 3	27 (17)
Stage 4	6 (3.8)
Unknown	96 (60.4)
Total	159 (100)

Age was not a risk factor for the development of brain metastases as there was no association between age and the presence of brain metastases ($r = 0.33$, $p = 0.31$). Brain lesions were strongly (significantly) associated with metastases in other organs ($p < 0.0001$). When the presence of brain lesions on ^{18}F-FDG PET/CT was looked at in relation to the site of primary lesions, hence head and neck, trunk, upper and lower extremities, no correlation could be found ($r = 0.29$, $p = 0.93$).

Even in patients with more than one primary site, there was still no correlation with the presence of brain metastases (r = 0.24, p = 0.65).

Figure 3: Metastatic sites in addition to brain and extremity lesions



Looking at metastases and extremities in relation with age (phi = 0.12, p = 0.20) and other metastases, there was also borderline significant correlation (p = 0.05). However, the presence of the primary site in the extremities correlated strongly with metastases in the same regions (r = 0.29, p = 0.004).

CHAPTER 4

Discussion

This study was performed to establish if there was a clinical impact of including the brain and extremities in the imaging of patients with malignant melanoma with ^{18}F-FDG PET/CT. The value of including the brain to the routinely used base of skull to mid-thigh field of view in patients with cancer yielded clinically significant findings in a study done by Abdemalik G et al (32). Their findings showed that detection of unsuspected brain metastases had a significant impact on patient management.

Our results showed that 6.7% of ^{18}F-FDG PET/CT studies had brain lesions classified as likely malignant or indeterminate (3.33% likely malignant; 3.33% indeterminate), which would not have been detected had brain acquisition not been acquired. Niederkohr et al demonstrated similar findings in their study of 296 studies in 173 patients, in which only 1.4% of all scans showed unanticipated abnormalities (5). The lower incidence rate from the study by Niederkohr et al found is however most likely because they further divided the most likely malignant brain lesions into 'expected' and 'unexpected' (either from clinical findings or from other imaging findings); and the percentage mentioned here is the unexpected group.

In our study, all 10 studies (6.7%) with suspected metastatic brain lesions had extracranial metastases detected on the usual field of view (base of skull to mid-thigh), and we found that the presence of brain lesions were strongly associated with metastases in other organs. Tan and Chatterton also found that all (12) patients with

suspected brain metastases had other multiple hypermetabolic sites in the usual field of view (38).

Thus in both our study and the study by Tan and Chatterton, there was no impact in clinical staging of adding dedicated brain images in the imaging of malignant melanoma with ^{18}F-FDG PET/CT as all patients with malignant brain lesions had extracranial metastases.

Clinical indications of deciding whether to add dedicated brain imaging in the ^{18}F-FDG PET/CT acquisition were explored in our study. Age was found not to be a risk factor for the development of metastases as we found no association between age and the presence of brain metastases.

When the presence of brain lesions in ^{18}F-FDG PET/CT was looked at in relation to the site of primary lesions, no correlation could be found. Even in patients with more than one primary site, there was still no correlation with the presence of brain metastases.

Tan and Chatterton also extrapolate that a change in clinical management is also unlikely (38). However, in our study, despite the lack of change in clinical staging, there was definite change in clinical management. The clinical notes of three out of six patients with brain metastases showed a definite change in management after the ^{18}F-FDG PET/CT with dedicated brain imaging. Two had added brain DXT in addition to their chemotherapy regimen. The other patient had a change in chemotherapy regimen. The clinical notes of four out of the 10 patients with brain metastases could not be retrieved unfortunately.

In our study, there were 37% (36/98) of studies with extremity lesions, of which three were visually likely benign on ^{18}F-FDG PET/CT. Twenty five studies had their primary tumour in the extremities with no additional lesion. Therefore, 8/98 (8%) studies were probably malignant.

Querellou et al and Niederkohr et al found overall lower limb abnormalities of 19% and 20% respectively (34) (5). These findings are lower when compared ours (37%). The reason might be due to sole inclusion of the lower limbs as the extremities in their imaging criteria, whereas in our study, extremities included the upper limbs as well where applicable depending on the site of primary lesion.

The lesions that were described as probably malignant in our study were found in 8% of studies, similar to Querellou et al who found 9% (34). Davidson et al and Niederkohr et al found 4% and 3% respectively (35) (5).

The study by Niederkohr et al showed a lower incidence percentage compared to our study, most probably because they looked at studies with unanticipated lower limb abnormalities (meaning that they excluded patients who were known with lower limb lesions either from known clinical history or other imaging modalities). This exclusion was not done in our study as well as in the study by Querellou et al.

Davidson and Sundram's study demonstrated a lower percentage probably due to their small sample size of 33 studies in 30 patients. Our sample size was 98 studies, Querellou et al was 174 studies and Niederkohr was 296 studies.

Five out of eight patients with suspicious lower limb lesions had other distant metastases; therefore in three out of the eight (37%) there was an isolated limb lesion.

Niedehkohr et al found that all patients with malignant lower limb lesions had other distant hypermetabolic metastatic lesions, therefore there was no isolated malignant lower limb lesion found (5).

Querellou et al found that all isolated lower limb lesions were subsequently proven to be benign, therefore no malignant isolated lower limb lesions were demonstrated in their study (34). The patients with malignant lower limb lesions had additional metastatic lesions in the usual field of view. The two latter authors further characterized the extremity lesions by histological correlation, clinical follow-up and further imaging studies but we did not. This might be the reason why they had no cases of isolated malignant lower limb lesions.

Our study furthermore looked at extremity lesions in relation with age and there was no correlation. However, the presence of the primary site in the extremities correlated strongly with metastases in the same regions.

The clinical files were missing in five out of the eight patients with suspected extremity lesions. The three patients that had clinical information available had no change in management.

The first patient had an isolated limb lesion and there was no change in management. The other two patients had additional distant metastatic lesions, also with no change in management.

Two out of eight patients (25%) with malignant lower limb lesions in Niederkohr et al's study had external beam radiation therapy as prophylaxis for pathological fractures, where external beam radiotherapy was applied to the tibia and distal femur (5). Despite this fact, they regard their findings to be unlikely to change clinical management significantly (5). In Querellou et al's study, there was no change in management in all 28 patients with malignant lower limb lesions (34).

Lazaga et al found only one malignant lesion in the extremities in a study of 200 ^{18}F-FDG PET/CT scans, which was subsequently proven to be an incidental squamous cell carcinoma unrelated to the melanoma (33). Similarly, Davidson and Sundram also found a single malignant lesion in the extremities, which was subsequently proven to be a giant cell tumour (35).

Overall, there was no change in management found in our study and by four other studies.

CHAPTER 5

5.1 Limitations

This study had several limitations, which might have influenced the outcome of some of the results. TNM stages were not available in all patients.

Very few patients did not have brain acquisitions as part of their study, whereas a significant number (more than 1/3) did not have extremities included in their study. This influenced the sample size and as a result could have influenced the true prevalence of brain and/ or extremity lesions detected, as these patients were excluded from the analysis.

Missing medical records in some patients may have affected the outcome with regards to ascertaining whether there was radiological and /or pathological correlation of unexpected brain and extremity lesions. We also could not confirm if there was change in management as a result of the presence of brain and extremity lesions on ^{18}F-FDG PET/CT, due to the missing patient medical records.

All the lesions classified as likely malignant and indeterminate were based on the ^{18}F-FDG PET/CT findings and not verified by either histology or clinical follow-up.

5.2 Conclusion

Our study demonstrated a 6.7% prevalence of brain lesions that were likely malignant or indeterminate, which would not have been detected had brain acquisition not been acquired. Our study also showed that all patients with brain metastases had other metastases elsewhere in the usual field of view, and hence brain acquisition did not result in a change in clinical staging. In three patients however there was a change in management. Although the overall impact of doing additional views of the brain did not upstage or downstage the patient, we feel that in view of the fact that in our study, 2% (3/150) of the patients had change in management, we cannot forgo brain acquisition even in patients with no known brain metastases.

The recommended protocol could be acquisition of brain views only in patients with additional metastatic lesions after the acquisition of the whole body view (base of skull to mid-thigh).

Our study also showed a 37% prevalence of extremity lesions, with the prevalence of probably malignant lesions being 17%. Only one patient had an isolated limb lesion, with no change in clinical stage or management. We thus feel that in view of the fact that in our study, none of the patients had change in management, the usual field of view (base of skull to mid-thigh) on ^{18}F-FDG PET/CT is possibly sufficient, as dedicated extremity views did not result in a change in the management. The exclusion of these views would significantly shorten the time of acquisition, resulting in increased PET/CT scan time for the imaging of more cases in a day. It would also lower radiation dose to the patient from the CT component of the PET/CT.

This then poses a question, of whether it would not be appropriate, based on the findings of this study, together with a strong published literature base, to change the acquisition protocol in our institution to limit acquisition of malignant melanoma to exclude additional views of the extremities and to only include brain acquisition where applicable to the usual field of view (base of skull to mid-thigh).

This proposition however needs to be validated by a prospective study.

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HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140258

NAME:
(Principal Investigator) Dr Olwethu Natahsa Mbakaza

DEPARTMENT: Radiation Sciences
Charlotte Maxeke Johannesburg Academic Hospital

PROJECT TITLE: What is the Imapct of Brain and Extremity inclusion in the Imaging of Malignant Melanoma with Flurine-18 Fluorodeoxyglucose Positron Emission Tomography (18 F-FDG PET/CT)?

DATE CONSIDERED: 28/02/2014

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Prof MDT Vangu

APPROVED BY:
Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 28/03/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS
To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate H
University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned res
and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, fro
research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to sul**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

yearly progress report

Principal Investigator Signature

M140258Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Office of the Chief Executive Officer
Tell: 011 488 3792
Fax: 011 488 3753
Email: lindiwe.mngomezulu@gauteng.gov.za
Date: 06 November 2013

Dr. Olwethu Mbakaza
University of Witwatersrand

Dear Dr. Olwethu Mbakaza

RE: "What is the impact of brain and extremity inclusion in the imaging of malignant melanoma with F-18 FDG"

Please note that permission to conduct the above mentioned study is provisionally approved. Your study can only commence once ethics approval is obtained. Please forward a copy of your ethics clearance certificate as soon as the study is approved by the ethics committee for the CEO's office to give you the final approval to conduct the study.

Approved/not approved

Ms. G. Bogoshi
Chief Executive Officer
Date: 7/11/2013